Guidance for Reviewers

Potency Limits for Standardized Dust Mite and Grass Allergen Vaccines: A Revised Protocol

DRAFT GUIDANCE

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GUIDANCE FOR REVIEWERS[1]

Potency Limits for Standardized Dust Mite and Grass Allergen Vaccines: A Revised Protocol

I. INTRODUCTION

The release limits for standardized dust mite and grass allergen vaccines are based on the performance characteristics of the competition Enzyme-Linked Immunosorbent Assay (ELISA) for the determination of the relative potency (RP) of these products. Using this assay, Center for Biologics Evaluation and Research (CBER) has required (21 CFR 680.3(e)) that all lots of these products be shown to be equivalent to the reference standard, with 95% confidence. Thus, the limits have been set at 0.70-1.43 for three determinations; when six determinations are made, the limits are 0.78-1.29.

These release limits will remain unchanged. However, CBER is establishing broader RP limits of 0.5 to 2.0 for its evaluation of standardized dust mite and grass allergen vaccines submitted to CBER for lot release. CBER lot release evaluations will be carried out with three replicates, using the competition ELISA recently re-validated by CBER. The manufacturers will be expected to maintain their current lot release limits, as detailed in their approved license applications. While these internal limits will continue to impose equivalence to reference at 95% confidence with either 3 or 6 replicates, CBER will only fail lots that, in its laboratory, fall outside the 0.5 to 2.0 limits.

In establishing broader release limits for CBER's testing of submitted allergen vaccines, CBER recognizes the predictable uncertainty associated with the submission of a product with a RP at or near the previously acceptable limits. The new CBER limits of 0.5 – 2.0 are statistically equivalent to applying a 95% confidence limit on the previous release limits for n = 3.

The potency limits for standardized allergen vaccines (Ref. 1, 2) should be based on acceptable ranges established in clinical studies. Three criteria appear to be important. The first, *therapeutic equivalence,* addresses the efficacy of allergen vaccines for immunotherapy. Thus, a RP range will have the property of therapeutic equivalence if, for the allergen vaccine in question, lots with relative potencies anywhere in that range have an equal likelihood of effecting clinical improvement in an immunotherapy trial. Likewise, *diagnostic equivalence* addresses the efficacy of allergen vaccines for in vivo diagnostics. Finally, *safety equivalence* reflects the likelihood of the safe administration of the vaccine for either diagnostic or therapeutic indications. The limits acceptable to CBER should fall within the narrowest of the equivalence ranges established by these criteria.

These clinical limits are discussed in sections II. through V. of this document. In addition, the variability of the potency of allergen vaccines can be considered in setting safe release limits; this is discussed in

[1] This guidance document represents the agency's current thinking with regard to potency limits for standardized dust mite and grass allergen vaccines. It does not create or confer any rights, privileges, or benefits on or for any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirement of the applicable statute, regulations, or both.

section VI. Finally, the current and broadened release limits are discussed in sections VII. and VIII.

II. DIAGNOSTIC EQUIVALENCE

The range of *diagnostic equivalence* is broad. The overwhelming majority of allergists use a qualitative grading system based upon the wheal size after percutaneous or intracutaneous skin testing (Ref. 3). In one study, the mean slope of the skin test titration curve was only 2.7 mm per 3-fold dose dilution for wheals. When standardized 10,000 and 100,000 BAU/mL grass extracts were compared, wheal size varied only minimally, but achieved statistical significance (P. Turkeltaub, unpublished data). For allergists who use erythema skin testing, the minimum detectable variability is only 3-4 fold (Ref. 4, 5) .

III. LITERATURE REVIEWED

Seven studies were chosen for analysis of therapeutic and safety equivalence, six of Amb a 1, one of Der p 1 (Ref. 6-12) (Table 1). Only three of the studies utilized allergen extracts that were rigorously standardized (Ref. 8-10) and three lacked any appropriate controls (Ref. 7-9). Nonetheless, each study provided some dose-response data on the efficacy and/or safety of allergen immunotherapy, although one (Ref. 9) was selected because of its observations on the physiologic effects of low dose immunotherapy. Six were analyzed for determination of therapeutic equivalence (Ref. 7-12) and three for determination of safety equivalence (Ref. 6,10, 12).

IV. THERAPEUTIC EQUIVALENCE

The range of equivalent *therapeutic* doses of allergen vaccines appears to be broad, and few investigators have performed detailed dose response evaluations in immunotherapy. Common allergy practice is to target the "maximum tolerated dose" as the therapeutic objective; on the other hand, controlled studies have suggested that maintenance dosing over a four-fold range of antigen is therapeutic (Ref. 1, 2, 13). Dose responses, when they have been performed, have been inexact. In each of the six studies chosen for this analysis, the investigators found that well-characterized allergen vaccines containing Amb a 1 or Der p 1 had a therapeutic effect over a broad dose range (Table 1). In three of the studies, symptom score improvements were examined after patients attained different allergen doses in their treatment. One study showed equivalence over a two-fold range (Ref. 8); another over a 14-fold range (Ref. 10); and the third over a 30-fold range (Ref. 12). Similarly, those studies that measured physiologic changes associated with allergen immunotherapy suggested equivalent responses over 12-fold (Ref. 11) and 1000-fold ranges (Ref. 7). The study by Hedlin et al., (Ref. 9) is notable in that multiple physiologic and immunologic changes associated with successful allergen immunotherapy appeared after achieving a dose of Amb a 1 of only 0.11 μg (cumulative dose 0.22 μg), a dose at least 10-fold less than what is normally associated with successful allergen immunotherapy.

V. SAFETY EQUIVALENCE

On the other hand, the range of *safety equivalence* of allergen vaccines may be narrower. In the

recent WHO position paper on allergen immunotherapy, panel members distinguished between the optimal dose and the maximum tolerated dose, and noted that the range between these may be highly variable (Ref. 1, 2).

Among the three selected studies that addressed the occurrence of systemic adverse reaction rates at different doses of allergen (Ref. 6, 10, 12), two included subsets of patients that warranted separate analysis. Van Metre et al., (Ref. 6) placed fifteen study subjects on standard, weekly immunotherapy, and eighteen subjects on a cluster regimen. Turkeltaub et al., (Ref. 10) described systemic reaction rates at various doses, as well as the rates of reactions severe enough to require treatment with subcutaneous injection of epinephrine. In our analysis of these two studies, these subsets were considered separately, even though there was some overlap of the patient groups described by Turkeltaub et al.

Further, some of the data were analyzed by the investigators on a per injection basis, and others on a per patient basis. Since these data cannot be combined or compared, they have been treated separately.

A. Linear Regression

For this analysis the adverse reaction rate is fitted against log dose. The fitted slopes and their standard errors are listed in Table 2. Thus, as a first estimate, one would expect a 4-11% increase in systemic reaction rates associated with each injection of an extract containing a ten-fold greater extract potency than the previous injection; on a per patient basis, the rise in systemic reaction rate would be 16-25%.

A more precise estimate is obtained by pooling the preceding slopes with weighting in inverse proportion to their standard errors. This yields an increase in the systemic reaction rate of 5.9% (per injection) or 19.6% (per patient) for a ten-fold increase in allergen dose.

B. Logistic Regression

To account for the fact that probabilities are bounded by 0 and 1 and tend to saturate at the extremes, fitting was also carried out with the logistic model

$$\ln\left(\frac{p_i}{1-p_i}\right) = m\ln(d_i) + b$$

where p_i is the probability of a reaction, and d_i is the dose. The interpretation of the fitting parameters necessarily differs from the prior analyses, in that incremental changes in reaction rates are not constant in all dosage ranges. Thus, a reasonable mean dose must be specified, and the increase in dose that would produce a given increase in systemic reaction rate calculated.

Defining d_0 as the geometric mean of the high and low doses, p_0, the probability of an adverse reaction at dose d_0, can be calculated directly from the equation after *m* and *b* have been determined. We then define the dose at which p_0 would be expected to increase by 0.05 as

$d_{0.05}$. This can be evaluated from the logistic equation:

$$\ln\left(\frac{p_0 + 0.05}{0.95 - p_0}\right) = m\ln(d_{0.05}) + b$$

The results of the fitting and subsequent determination of the ratio $d_{0.05}/d_0$ are listed in Table 3. This analysis shows increasing the dosage between 2.4 and 5-fold (an average of 4-fold) leads to a 5% increase in the adverse reaction rate for the per injection data; for the per patient data, 1.5 to 2-fold (an average of 1.7) dose increases lead to 5% adverse reaction increases.

C. Safety Equivalence: Summary

Unfortunately, little else has appeared in publication that can shed light on the question of safety equivalence. While the data in Table 1 indicate that increases in RP typically lead to increases in adverse systemic reactions to immunotherapy, the range is quite varied and the study designs are suboptimal. Clearly, studies with better design (placebo-controlled, double blind with well-defined, highly sensitive subjects and well-characterized products with FDA acceptable standard of potency) would be preferable and are needed.

It should be noted that only safety data within therapeutically equivalent dose ranges were analyzed. Thus, while all of Haugaard's (Ref. 12) data were included for analysis, the lowest data points in Turkeltaub (Ref. 10; 0.003 μg) were excluded.

It is not possible, based on these studies alone, to assign a definite value to the increased risk of systemic reaction associated with increased potency. A conservative estimate of an acceptable increase in potency may be attempted, if we assume that the increase in the adverse reaction rate upon an increase in dosage should be less than 5%, and that the final reaction rate should not be much greater than 5-10%. Reaction rates in this range may be an unavoidable feature of curative immunotherapy with native antigens. At best, this analysis shows that the clinical data available suggest that a four-fold variation in allergen vaccine potency yields an acceptably small increase in systemic reaction rates.

VI. LOT-TO-LOT VARIATION IN ALLERGEN VACCINE POTENCY

The aggregate consistency of manufactured lots might also be taken into account when establishing testing limits. For example, if typical lot-to-lot consistency were very high and well within clinical limits, then testing protocols could be adjusted to eliminate outliers while rarely failing lots whose RP is close to unity. On the other extreme, if the distribution of lots were broad, then stastical equivalence to the reference would be appropriate.

A. Sample Variance

The observed variability of a group of lots of an allergen vaccine is a function of the sample variability and the variability of the assay. Defining the densities of the sample, assay and

observed distributions $f_s(x)$, $f_a(x)$, and $f_{obs}(x)$, respectively, the relation between them is (Ref. 14):

$$f_{obs}(x) = \int_{-\infty}^{\infty} f_s(t)\, f_a(x-t)\, dx$$

Assuming that the sample and assay densities are normal with variances σ_s^2 and σ_a^2, respectively, $f_{obs}(x)$ is normal with variance

$$\sigma_{obs}^2 = \sigma_s^2 + \sigma_a^2$$

An estimate of the variability of lots submitted to CBER can be obtained from the failure rate of the submitted products and the intrinsic variability of the competition ELISA that was used to test the products. Between 1995 and 1997, ten different manufacturers submitted 412 lots of grass pollen extract in support of licensure. Likewise, between 1995 and 1999, eleven manufacturers submitted 91 lots of licensed dust mite extracts for approval. The failure rates of these lots were analyzed to determine lot variability.

For the grasses, 51 of 412, or 12.4%, failed lot release specifications. Of these, 29 were above the upper limits, and 22 fell below the lower limits. Assuming that the submitted lots are normally distributed about the reference (in x = log RP), half would have failed high implying that 93.8% were below the upper limit, $x' = \log 1.53 = 0.1847$:

$$\int_{-\infty}^{x'} f_{obs}(x)dx = 0.938$$

The standard deviation of f_{obs} may be obtained by transforming to the standard normal, in which case, $z' = x'/\sigma_{obs}$. From a table of the cumulative normal distribution, z'=1.54, or $\sigma_{obs} = 0.120$. The standard deviation of the assay with three replicates, σ_a is $0.1375/\sqrt{3} = 0.0794$. It then follows that $\sigma_s = 0.090$.

For standardized dust mite allergen vaccines, 6 of 91 failed (3 high and 3 low), the preceding analysis yields z'=1.84 and σ_s = 0.061.

B. Potency Range

The change in RP when switching bottles can be estimated from the absolute difference of two samples picked at random from a distribution. This is a special case of determining the range, *R*, which is defined by the difference between the highest and lowest of *n* samples taken from a distribution with density *f(x)* (Ref. 14). For *n*=2, the density, $f_R(r)$, is given by

$$f_R(r) = \begin{cases} 2\int_{-\infty}^{\infty} f(x) f(r+x) dx & r > 0 \\ 0 & r < 0 \end{cases}$$

The average range is then calculated from

$$\langle r \rangle = \int_0^{\infty} r\, f_R(r) dr$$

It is also useful to denote the quantity r' such that

$$\int_0^{r'} f_R(r) dr = 0.95$$

That is, 95% of the values of the range are less than r'.

For a normal (or Gaussian) density with variance σ^2, the density, average, and 95% maximum for the range are as follows:

$$f_R(r) = \left(\sqrt{\pi}\sigma\right)^{-1} \exp\left(-r^2 / 4\sigma^2\right)$$

$$\langle r \rangle = \sqrt{(2/\pi)}\,\sigma \approx 0.8\,\sigma$$

and $$r' = \sqrt{2} \times 1.96\,\sigma \approx 2.8\,\sigma$$

From the values of σ calculated above, $\langle r \rangle = 0.0718$ and $r' = 0.249$ for the grass extracts. These ratios are in log RP. Thus, the anticipated mean change in RP upon switching bottles is ($10^{0.0718}$ - 1), or 18%. Likewise, 95% of the potency shifts will be less than ($10^{0.249}$ - 1), or 80%.

For the mites, $\langle r \rangle$ = 0.049, and r' = 0.171, implying that the mean change in RP is 12%, and that potency shifts will be less than 48% in 95% of cases.

VII. CURRENT CBER RELEASE LIMITS

Given the uncertainty of the true clinical limits for the accuracy of allergen vaccine content, CBER has, in the past, utilized the accuracy of the test used to measure RP as the *de facto* limits for vaccine approval. Thus, the 95% Confidence Interval (CI) limits for the Radioallergosorbent Test (RAST) inhibition assay were 0.46 to 2.12. These limits were acceptable since they were equivalent to the erythema diagnostic equivalence data. The competition ELISA is more accurate and, using this assay, CBER narrowed the 95% CI limits to 0.70-1.43 for three determinations; when six determinations are made, the limits are narrowed further to 0.78-1.29. The strength of CBER's current approach is that it decreases the

likelihood that a mite or grass allergen vaccine with a RP substantially different from 1.0 will be released in the US market.

VIII. BROADENED RELEASE LIMITS

The internal release limits that establish equivalence to the reference at 95% confidence will remain unchanged. We are establishing RP limits of 0.5 to 2.0 for standardized dust mite and grass allergen vaccines submitted to CBER for lot release. CBER lot release evaluations will be carried out with three replicates, using the competitive ELISA recently validated by LIB. *The manufacturers will be expected to maintain their current lot release limits.* These internal limits now impose equivalence to reference at 95% confidence with either 3 or 6 replicates, depending on the manufacturer. CBER will consider as acceptable lots that fall within the 0.5 to 2.0 limits. This represents an expansion of the RP limits that CBER would find acceptable.

In initiating this change, we also expand the RP limits for the shelf life of the product, provided the initial release data fall within the internal lot release specifications. Current shelf life limits are 0.568-1.759, as follows from a Bonferroni correction (Ref. 15, 16). Hence, the expansion to 0.5 to 2.0 allows for a small degree of decay over the shelf life of the standardized allergen vaccines currently licensed. Current data suggest that these glycerinated vaccines are stable; if further data confirm this stability over the current three-year dating period, the acceptable manufacturers' internal limits may be broadened.

The likelihood of lot failure by CBER depends on the manufacturer's internal specifications (the limits and the number of internal replicates). A product subjected to 6 replicate evaluations by the manufacturer, with a result falling between 0.776 and 1.288, has no greater than a 2.5% chance of failure. On the other hand, a product subject to only three replicates has a 9.8% chance of failure (Table 4).

While the preponderance of studies suggests that a ten-fold range of RP would be acceptable from a therapeutic point of view, we believe that the four-fold range is preferable because of safety concerns. Furthermore, future studies comparing the efficacy of allergen vaccines will be difficult to interpret if a ten-fold range of potency becomes the accepted norm. Finally, the four-fold range is well within the established capabilities of the allergen manufacturers using current techniques and standards.

The 0.5-2.0 limits are the same as those proposed by the European Union (EU) and, thus, nominally achieve harmonization. However, there are important differences. The procedure established here enforces tighter internal limits on the manufacturer and follows with a confirmatory test by CBER. This greatly reduces the probability that the true RP of any product falls outside the 0.5-2.0 range, *even if it were not tested by CBER.* The EU document, in contrast, does not stipulate either test methodology or confidence level. Hence, according to the EU standard, a lot tested by the manufacturer as 0.51 is acceptable as long as it passes subsequent testing by the appropriate regulatory agency. This would not be the case using the limits described in this draft guidance document.

In establishing broader release limits for CBER's testing of submitted allergen vaccines, we recognize the predictable uncertainty associated with the submission of a product with a RP at or near the previously acceptable limits. The new CBER limits of 0.5 – 2.0 are statistically equivalent to applying a

95% confidence limit on the previous release limits for n = 3. Thus, the 95% confidence lower limit of an allergen vaccine with a RP of 0.699 is $10^{\log 0.699-1.96\sigma/\sqrt{n}}$, or 0.488. Likewise, the 95% confidence upper limit of an allergen vaccine with a RP of 1.431 is $10^{\log 1.431+1.96\sigma/\sqrt{n}}$, or 2.047.

The advantages of adopting these broadened release limits are:

1. We establish a system in which the limits are based upon the human clinical response to allergen vaccines.
2. We differentiate between limits based on clinical data and those based on the accuracy of the in vitro assays used to measure RP. This distinction will be especially important as our in vitro methods become more accurate in the years to come.
3. The 0.5 to 2.0 limits are within the previously acceptable limits based on the RAST inhibition assay. These broader limits were not associated with any increased safety concerns.
4. Manufacturers that perform six replicate evaluations are extremely unlikely to experience lot rejection by CBER.

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TABLE 1

Summary of cited studies

Allergen	Dose response endpoint(s)	Number of patients in active group	Dose range	Observations	Reference	Notes
Amb a 1	Systemic reactions	33	Up to 18.7 μg	7/15 patients undergoing the weekly regimen, and 10/18 patients undergoing the cluster regimen, experienced systemic reactions at doses ranging from 0.13 to 13.1 μg.	6 Van Metre, et al.	Commercial lyophilized product, compared with purified reference allergens by RID. Placebo control.
Amb a 1	Antibody responses	51	Up to 93.5 μg	Threshold doses for antibody responses varied 1000-fold.	7 Creticos et al. 1984	Commercial aqueous extract. Standardization uncertain. No placebo or untreated control.
Amb a 1	Symptom scores and nasal challenge	11	0.6, 6 and 12 μg	0.6 subtherapeutic; 6 and 12 equivalent and effective.	8 Creticos et al. 1989	Aqueous product prepared by investigators from ragweed pollen, and compared with CBER reference standard by RID and crossed immuno-electrophoresis. No placebo or untreated control.
Amb a 1	Nasal challenge and antibody responses	40	Up to 0.11 μg	Measurable decreases in Amb a 1-induced nasal histamine and TAME release; decrease in skin test reactivity; and increase in ragweed-specific IgE after a cumulative Amb a 1 dose of only 0.22 μg.	9 Hedlin et al. 1989	Commercial aqueous extract, defined Amb a 1 content. No placebo or untreated controls.
Amb a 1	Symptom scores and systemic reactions	129	0.003, 0.3, 1.8, 2.25 and 4.2 μg	0.003 dose ineffective; all other doses effective. Systemic reaction rate (reactions/ injection) using standard protocol: 2.1% at 0.8 μg and 5.6% at 4.2 μg. Rush protocol: 2.3% at 0.003 μg, 2.8% at 0.3 μg, 22% at 2.7 μg, 11% at 4.3 μg. Percent of patients requiring epinephrine: 7.5% when the maximum dose was 0.3 μg, 15% at 0.82 μg, 23% at 2.7 μg, 30% at 4.2 μg, and 25% at 4.3 μg.	10 Turkeltaub et al. 1990	Aqueous products analyzed by RID, RAST inhibition and parallel-line bioassay, and standardized by comparison with CBER reference standard. Untreated control, no placebo control.
Amb a 1	Seasonal and post-challenge nasal eosinphilia	89	2 and 24 μg	High and low doses effective in the challenge phase of study. In the seasonal phase, only the higher dose was effective.	11 Furin et al. 1991	Source and standardization of ragweed extract uncertain. Untreated control, no placebo control.
Der p 1	Symptom scores and systemic reactions	81	0.7, 7 and 21 μg	All three doses therapeutically equivalent. Systemic reaction rate (reactions/injection) 0.56% at 0.7 μg, 3.30% at 7 μg, and 7.10% at 21 μg.	12 Haugaard et al. 1993	Commercial aqueous (skin testing) and alum adsorbed (IT) extracts. Compared to an internal standard by RAST inhibition, immunoelectrophoresis, and bioassay (HEP method). Untreated control, no placebo control.

TABLE 2

Slopes and their standard errors (SE) from linear fits of adverse reaction rates vs. log dose. Unless otherwise noted in the text, all data from each report were analyzed. The final 2 columns list weighted averages (over all sources for each study design) for the % increase in adverse reaction rates expected for ten-fold and four-fold increases in dose, respectively.

Study design	Source	Slope	SE	% increase in adverse reaction (ten-fold dose)	% increase in adverse reaction (four-fold dose)
Per injection	Haugaard et al. 1993 (12)	4.2	1.3	5.9	3.5
	Haugaard et al. 1993 (12) (maintenance)	9.1	3.8		
	Turkeltaub et al. 1990 (10)	11.1	10.9		
Per patient	Van Metre et al. 1982 (6) (weekly)	25.3	2.4	19.6	11.8
	Van Metre et al. 1982 (6) (cluster)	16.4	2.0		
	Turkeltaub et al. 1990 (10) (epinephrine)	17.2	2.2		

TABLE 3

Summary of logistic regression. Fitting parameters, *m* and *b* are defined by Eq. (1); d_0 is the geometric mean of the highest and lowest doses used in each study; and p_0 is the probability of an adverse reaction at d_0 calculated from Eq. (1). As discussed in the text and defined by Eq. (7), $d_{0.05}$ is the estimated dose in which the probability of an adverse reaction increases by 0.05 over p_0. Units of *m*, *b* and d_0 are omitted for clarity.

Study design	Source	*m*	*b*	d_0	p_0	$d_{0.05}/d_0$
Per injection	Haugaard et al. 1993 (12)	0.77	-4.98	4.69	0.02	4.6
	Haugaard et al. 1993 (12) (maintenance)	1.12	-5.11	4.69	0.03	2.4
	Turkeltaub et al. 1990 (10)	0.29	-2.33	1.52	0.10	5.0
Per patient	Van Metre et al. 1982 (6) (weekly)	0.67	-2.11	4.25	0.24	1.5
	Van Metre et al. 1982 (6) (cluster)	0.29	-0.49	4.25	0.48	2.0
	Turkeltaub et al. 1990 (10) (epinephrine)	0.56	-1.76	1.64	0.19	1.7

TABLE 4

Probability that CBER will pass or fail an allergen vaccine with a submitted RP (RP) of 0.5 to 2.0. Note that the proposed standard will require manufacturers to continue submission of vaccines within the 95% CI of RP = 1, indicated in **bold** typeface, for N_{manu} = 3, or for N_{manu} = 6.

N(manu) = 3			
RP	P(fail) low	P(fail) high	P(pass)
0.5	0.500	0.000	0.500
0.6	0.240	0.000	0.760
0.699	**0.098**	**0.000**	**0.902**
0.7	0.097	0.000	0.903
0.8	0.035	0.000	0.965
0.9	0.011	0.001	0.988
1	0.004	0.004	0.993
1.1	0.001	0.010	0.988
1.2	0.000	0.024	0.976
1.3	0.000	0.048	0.952
1.4	0.000	0.084	0.916
1.431	**0.000**	**0.098**	**0.902**
1.5	0.000	0.133	0.867
1.6	0.000	0.194	0.806
1.7	0.000	0.265	0.735
1.8	0.000	0.342	0.658
1.9	0.000	0.421	0.579
2	0.000	0.500	0.500

N(manu) = 6			
RP	P(fail) low	P(fail) high	P(pass)
0.5	0.500	0.000	0.500
0.6	0.208	0.000	0.792
0.7	0.066	0.000	0.934
0.776	**0.025**	**0.000**	**0.975**
0.8	0.018	0.000	0.982
0.9	0.004	0.000	0.995
1	0.001	0.001	0.998
1.1	0.000	0.004	0.996
1.2	0.000	0.011	0.989
1.288	**0.000**	**0.025**	**0.975**
1.3	0.000	0.027	0.973
1.4	0.000	0.056	0.944
1.5	0.000	0.099	0.901
1.6	0.000	0.159	0.841
1.7	0.000	0.234	0.766
1.8	0.000	0.319	0.681
1.9	0.000	0.409	0.591
2	0.000	0.500	0.500

$$\text{P(pass)} = \int_{\log 0.5}^{\log 2.0} f(x)dx$$

where x is the log of the RP calculated by the manufacturer (with N_{manu} replicates) and subsequently by CBER (with 3 replicates). $f(x)$ is a normal distribution in log RP with variance,

$$\sigma^2 = \sigma_{CBER}^2 + \sigma_{manu}^2$$
$$= \frac{(0.1375)^2}{3} + \frac{(0.1375)^2}{N_{manu}}$$

and 0.1375 is the standard deviation in log RP of the current CBER ELISA.